AN AIDS

It's possible.

VACCINE

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THIS PAGE: JOEL STETTENHEIM/ SABA; OPPOSITE: GIDEON MENDEL/ NEWWORK/ MATRIX

So why isn't it being done?

By Mark Schoofs

How can HIV be stopped? Medical science has never cured a viral illness, and the AIDS virus hardly looks like the exception. Therapies now in the pipeline promise only to delay death. They are also wildly expensive for the Third World, where 90 per cent of new infections are occurring and where annual health care spending can be less than five dollars per person.

Educational campaigns stand even less of a chance. Among American gay men—one of the best-informed communities anywhere—the virus continues to spread at a despairing rate. An urban gay man in his twenties can expect to see half his generation infected by the time he's in his fifties. In developing countries, illiteracy and poverty make education downright quixotic.

As it stands, the World Health Organization estimates that 18.5 million people are already infected, and another person contracts HIV every nine seconds.

The best hope for stopping the pandemic is the same as it was for smallpox and polio: a vaccine. But despite sound scientific reasons to believe an AIDS vaccine is possible, the effort to develop one has been largely abandoned by industry, neglected by activists, and slighted by government.

A recent report by the Rockefeller Foundation, a leader in international health, estimates that, in 1993, spending on an AIDS vaccine—public and private, worldwide—was just under $160 million. That's less than the latest Kevin Costner movie.

Stunning results in monkeys, as well as surprising immune responses in humans, have convinced most researchers that an AIDS vaccine can be made. Nevertheless, a paralyzing pessimism, based on the perception that a vaccine is virtually impossible, has slowed the search.

No vaccine has yet been tested for efficacy in humans. Numerous Phase I and Phase II safety trials have occurred, but they are far too small to be conclusive. And few of the many vaccine strategies have been tested in humans at all. "Because we have never evaluated a vaccine," says John McNeil, clinical director of the army's AIDS vaccine program, "we have not gotten to the point where we know whether the science is a problem."

What we do know is that HIV poses a lot of *potential* problems. Dr. Maurice Hilleman led the vaccine division at pharmaceutical giant Merck for almost 30 years, where he developed more vaccines than anyone in history: measles, mumps, rubella, and hepatitis B are his biggest trophies. But he says they look easy compared to AIDS: "My God, here's a disease for which there is no recovery."

That's worrisome because vaccines don't attack a virus on their own. Instead, they train a person's immune system by mounting an attack with harmless viral impostors. Until very recently, vaccinologists used killed virus, as Jonas Salk did with polio, or they "attenuated" the virus, removing key parts so that it was alive but powerless to cause disease, as Albert Sabin did with his competing polio vaccine.

The inoculation for hepatitis B marked the first time researchers engineered a vaccine by isolating specific viral "subunits" that actually provoke an immune response. But despite this advance, the principle of vaccination remains the same as it was thousands of years ago, when Chinese doctors blew pulverized smallpox scabs through bone tubes into the noses of healthy patients: Prime the immune system so it's ready when it encounters the virus in the wild.

But with HIV, the immune system seems to have met its match. It doesn't eliminate the virus, and although some "long-term survivors"

Scenes from AIDS in Africa: Ninety per cent of new infections are occurring in the Third World.

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stave off disease for 15 years or more, they appear to be a tiny fraction of infected people. Ultimately, even they might succumb to the disease. "We may have to improve on nature," says Duke University's Dani Bolognesi, a leading AIDS vaccine researcher.

Because people don't recover, scientists don't know what part of the immune system to target for enhancement. Should they attempt to elicit neutralizing antibodies, which attack free-floating virus in the bloodstream? Or should they try to rev up "cytotoxic" response, the other main arm of the immune system, which targets infected cells? Many researchers believe both are needed, but getting the right balance is tricky because, like a biological seesaw, raising antibodies tends to lower cytotoxic response and vice versa. And because HIV attacks the immune system itself, stimulating the wrong kind of response could abet the virus's invasion of the body.

Another potential problem is that 80 per cent of all HIV infections occur sexually, which means that the virus usually enters through mucosal tissues in the vagina, rectum, or mouth. It's possible that HIV could be stopped there, and also that it must be stopped there, before it spreads through the body. But little is known about mucosal immunity—or for that matter about the immune system in general. Some experiments suggest that protection against HIV may come from immune responses that have not yet been identified.

Assuming the right response could be mobilized, it would have to protect against a vast range of strains. HIV-1 is one of the most mutable viruses known. (There's also HIV-2, which is less virulent, less transmissible, and much less common.) HIV-1 has eight major genetic subtypes, called "clades," and more than 660 catalogued variants. In some areas of the world, several clades circulate among the population; but even in North America, where one subtype predominates, the others are just a plane ride away. Finally, in several African countries, scientists recently discovered an entire additional HIV-1 group, with its own clades. This immense and rapid variability is reason enough to rush a vaccine.

Another impediment is the lack of an ideal animal model. Chimpanzees get infected with HIV, but they do not progress to AIDS and can even eliminate some strains of virus on their own. Many researchers believe monkeys such as the rhesus and macaque are the best model, even though they don't get infected with HIV. Instead, they are susceptible to the closely related simian virus SIV, and they get sick with an AIDS-like disease.

Experiments with these monkeys counter the doomsayers. In separate protocols by different research teams, a vaccine protected the animals against SIV. It worked against virus that was both free-floating and in cells, against intravenous and mucosal transmission, and against different viral strains. The vaccine's immunity was also long-lasting, protecting the monkeys against a "challenge" infection more than two years later.

The vaccine used a live attenuated virus, which the vast majority of scientists consider too dangerous for a retroviral vaccine. Even if it never caused AIDS, attenuated HIV could induce cancer or neurological disease, as retroviruses often do. Nevertheless, these experiments offer rock-solid evidence that a vaccine is possible.

There are other reasons for optimism. Recent data from the World Health Organization's project to describe the genetic variation of HIV suggest that, although the virus varies tremendously, the parts that are vulnerable to immune attack might be fairly "conserved." Antibody sera from some people infected with one strain of HIV neutralized many other strains, even across clades. The significance of this is not yet fully understood, but WHO's vaccine chief, Dr. Jose Esparza, says, "We cannot assume today that the genetic variability of HIV-1 is an unsurmountable obstacle."

Perhaps the strongest hope lies in the immune response of human beings. While it is true that people do not fully recover from HIV infection, they do mount a powerful counterattack. Indeed, most people succumb only after years. "If it's a horse race and all you have to do is tip the balance," says Hilleman, "maybe that's possible."

Indeed, a few people seem able to ward off the virus. Separate research teams have found prostitutes in Kenya and Gambia who have been repeatedly exposed to HIV for years but have not become infected. The most probable explanation, concluded one study, "is that they have been immunised by exposure to HIV." In fact, researchers found that many of these women had cytotoxic resistance tailored specifically to HIV; similar immune responses have been found in exposed but uninfected gay men, drug users, health care workers, and babies born to HIV-positive mothers.

It remains unknown whether such resistance is enough to protect most people, or how to induce it artificially. The devil is in the details. But together with the successfully vaccinated monkeys and the vigorous immune response of almost everyone, these resistant people constitute a powerful antidote to pessimism.

Not powerful enough, however, for the private sector. Early on, at least four large pharmaceutical companies and a bevy of biotechnology firms threw their hats in the ring, in part because the hepatitis B vaccine proved that the safer and supposedly cheaper re-

combinant technology could work. But as an AIDS vaccine has proven more stubborn, the private sector has fled.

Of the big companies, only Pasteur Mérieux—the world's preeminent vaccine producer—has made a substantial effort. It is pursuing many different approaches, four already in clinical trials, and the company says it is devoting one-fifth of its R&D budget to the effort. However, Pasteur Mérieux was recently bought by Rhône-Poulenc, and some observers worry that the multinational chemical corporation might replace the Mérieux family's humanitarian philosophy with the same bottom-line mentality that is driving most companies and investors out of the AIDS vaccine business.

Private funding has completely dried up for the effort at Therion Biologics, a small firm whose simian prototype vaccine has shown the ability to induce both antibody and cytotoxic response. Therion's program, now half its former size, subsists solely on U.S. government research funds. Three years ago, Bristol-Meyers Squibb substantially cut back its program, despite encouraging results in monkeys. Last year, Genentech and BioCine (a joint venture of Chiron and Ciba-Geigy) slashed their programs by more than 80 per cent, after a controversial decision by a federal scientific panel nixed large human efficacy trials of their vaccines. The two companies had each spent between $50 million and $100 million shepherding their products, both based on a viral envelope protein called gp120, through Phase I and II safety trials. Last year was also when Merck and its small partner Repligen suspended work on a product they finally concluded wouldn't work, after spending perhaps $30 million.

At least Merck retains an in-house research team, even if most analysts believe it's small. Burt Dorman's little biotech firm, Acrogen, has "not yet wet a test tube." For three years, Dorman has been trying to raise $5 million to make a whole-killed vaccine, like the kind Salk made for polio. (When he died, Salk was working on a therapeutic AIDS vaccine—one that would be given to already-infected people as an immune booster—using a variation of the whole-killed approach.)

Dorman can't believe that, more than a decade into the epidemic, almost no one in industry or government is seriously pursuing a whole-killed approach to a preventative vaccine (see sidebar, "Not My Job"). After all, that's the method used for about a third of all viral vaccines, and Dorman used it to develop several veterinary immunizations. In addition, that approach has worked in cats, protecting them against a leukemia retrovirus with similarities to HIV. "It's simple common sense to start with things that have worked before," he says.

But investors, says Dorman, weren't excited by the "40-year-old technology," even though SIV studies were encouraging. Monkeys inoculated with a whole-killed vaccine got infected, but they lived much longer than uninoculated controls, and they were less infectious. No existing vaccine completely repels infection—instead they prevent the onset of disease—and many scientists think "sterilizing immunity" will also be impossible for HIV.

But even before discussing the science, Dorman had to counter "the standard litany" of objections: "Vaccines are generally perceived to be bad business, and AIDS vaccines are seen to be the worst. You would invest a lot of money and time to get it licensed, and if you got it licensed there'd be a lot of pressure to give it away, especially to the Third World. Even if you gave it away, you'd still have the liability: If the vaccine were nothing but salt water, someone would get sick the day after he got injected, and you'd get sued." Even a group of people who wanted to *donate* money got scared off by the specter of liability.

The Rockefeller report noted that the private sector accounts for about 40 per cent of general medical research, but only about 15 per cent of research into an AIDS vaccine—and that estimate was made before several of the biggest private efforts fizzled. "AIDS vaccines," says Therion president Dennis Panicali, "have lost their appeal on Wall Street."

In this sense, AIDS is hardly unique. In the late 1970s, more than a dozen major companies made vaccines. Now there are only four. Even though vaccines are the most cost-effective public health measure ever invented, they generate little profit. Worldwide, vaccines account for less than 1 per cent of all prescription sales. The leading ulcer medication does better than all vaccines combined.

Development can easily last a decade and cost more than a quarter-billion dollars. Everything from lab work to quality control costs more, in part because vaccines tend to be made from fragile biological material, as opposed to drugs, which are typically made from inert chemicals. Most importantly, vaccines face far higher hurdles than therapeutic drugs in getting onto the market. If a drug for a life-threatening illness can demonstrate that it probably works, it can usually get accelerated approval, even with serious side effects. AZT, which is now known to have only a marginal benefit when taken by itself, was originally approved on this basis, and the drug has rung up almost $2 billion in sales since 1989.

Stunning results of experiments in monkeys, as well as surprising immune responses in humans, have convinced most researchers that an AIDS vaccine can be made.

Because a vaccine is given to healthy people, it must meet much stricter standards. (It is a common belief among vaccinologists that the Sabin live-attenuated polio vaccine could not win a license from the Food and Drug Administration today, because it causes polio in a tiny fraction of its recipients.) In fact, vaccine developers typically can't predict if their product will be licensed until the completion of double-blinded placebo studies that involve thousands of participants and span years.

With AIDS, this could take a particularly cruel twist. A vaccine that hit the jackpot of "sterilizing immunity" could be tested in a trial lasting perhaps two or three years—not much longer than for other diseases. But trials for a vaccine that prevents disease might have to last a decade, perhaps longer.

Brandon Fradd, an M.D. turned securities analyst, has been watching AIDS vaccines since the late 1980s, first for Shearson Lehman Hutton and now for Montgomery Securities. Because of the unpredictable—but certainly astronomical—R&D costs for an AIDS vaccine, he says the industry won't gamble until science can demonstrate that "if you do X, Y, and Z, you pretty much have it." In other words, the private sector rarely invests in vaccine research until the hard questions have already been answered and it can smell profit.

When the market fails to provide an important public service, government is supposed to step in. But

Congress and the Clinton administration have actually worsened the vaccine environment.

Last year, the Vaccines for Children program greatly increased the amount of vaccine the government buys, and it set a cap on what it pays. Although the program doesn't include AIDS, it sets a profit-withering precedent that deters investment in all vaccines. That's why prominent researchers have joined industry executives in opposing it.

What the government should do, these experts say, is guarantee to purchase a licensed AIDS vaccine at a price that guarantees a healthy profit. Even better, it could prime the pump by creating a public-private consortium that would share R&D costs. The government has done this before: Sematech, which carries out semiconductor research, spends $180 million per year, half provided by the Defense Department. Similar proposals have targeted the vaccine industry, but they have been ignored.

Government could also offer massive tax incentives for vaccine development, extend the patent life on a successful product (giving the company longer to earn back its R&D costs before competitors can copy the formula), and exempt an AIDS vaccine from liability lawsuits. One of the government's few real achievements is the National Vaccine Injury Compensation Program. It effectively precludes lawsuits arising from the small number of serious adverse reactions caused by childhood vaccines, and it compensates victims from a fund supported by a small tax on vaccine sales. But the program does not include HIV.

Fradd asks, "Has the government gone out of its way to make development of a vaccine so cheap that you'd be foolish not to give it a shot? No." Meanwhile, the federal government will spend $4.2 billion this year on medical care and social services for people with HIV, private insurers will pay out another $1.5 billion, and the economic value of labor lost to AIDS will be $20 billion.

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By contrast, the government has earmarked a mere $149 million this year to search for a vaccine. About $21 million goes to a Department of Defense program, and the rest goes to the National Institutes of Health.

Although NIH is often criticized (see sidebar), its research is indispensable, and it subsidizes academic labs and private companies alike. Even Pasteur Mérieux, the biggest vaccine firm, says that without aid from the NIH and its much smaller French-government equivalent, it would be unable to continue its effort.

But NIH allocates just 9 per cent of its AIDS budget to vaccines, a smaller slice of the pie than *any* AIDS research category. Therapeutics garners 35 per cent; Etiology and Pathogenesis (how disease begins and develops) 23 per cent; Natural History and Epidemiology 14 per cent; and Behavioral Research 12 per cent. (The remaining 7 per cent goes mainly to support services.)

"You're asking the question, 'Are we doing enough for vaccines?' " says Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, the NIH branch that conducts the most AIDS vaccine research. "*Enough* is a very elusive word." He points out that, in science, categories often overlap: understanding pathogenesis, for example, can aid the search for a vaccine. He adds that the budget for therapeutics is inflated by clinical trials, the most expensive part of research. More of those trials are occurring for treatments than for vaccines, he says, because drugs have advanced faster. But even subtracting the cost of trials,

NOT OUR JOB

Why Can't the Government Make a Vaccine?

Whose job is it to make an AIDS vaccine? "If you ask, you'll hear it's the mission of a combination of organizations," says Wayne Koff, who used to run the AIDS vaccine program at the National Institute of Allergy and Infectious Diseases, and now does the same for a biotech company. "But it's probably the mission of nobody."

Vaccine activist Don Francis

BART EVERLY

Indeed, only the U.S. army says its mission is to make a vaccine, test tube to syringe. But its AIDS vaccine budget is a paltry $21 million. By contrast, the National Institutes of Health spends $128 million, more than half of all the AIDS-vaccine money in the world. The NIH funds almost every academic vaccinologist, conducts its own research, and subsidizes the R&D of private companies. "If you didn't have NIH," says the renowned vaccinologist Maurice Hilleman, "you'd really be out there without a paddle."

But NIH provides only theoretical, or "basic," science, which private companies are supposed to churn into tangible products. Trouble is, industry has largely fallen out of the equation, leaving the AIDS-vaccine pipeline almost empty. "We have the infrastructure to do two to three times as many Phase I and II trials as we're doing now," says Alan Schultz, a top administrator of NIAID's vaccine program, "but we don't have products."

NIAID, which receives almost two-thirds of the NIH's AIDS vaccine budget, is trying to coordinate more effectively with industry and is considering manufacturing prototype vaccines. But these steps won't solve the deeper problems: the NIH moves with maddening lethargy, its endeavors are loosely coordinated, and it slights empirical research.

NIAID director Anthony Fauci concedes the bureaucratic pace is "very frustrating." Citing contracting laws that require months for advertising, review, and other protections against cronyism, he explains: "When one of my colleagues gets a terrific idea and I push it through—I mean, I'm standing there with a whip saying, 'Let's go, let's move'—it still takes a year" until lab work begins.

Very little work at the NIH is assigned. Instead, most research is "investigator initiated," meaning individual scientists create their own projects that peer panels approve. Defenders of this system argue against directing research more aggressively, because no one knows for sure which course to take. But some guidance is given through "solicited" work, in which the NIH defines an important topic and researchers propose experiments in that area. There are also "unsolicited" projects, wherein scientists submit proposals out of the blue: "You can never rule out that some scientist somewhere is going to have a brilliant idea that will turn the field on its head," says Patricia Fast, associate director of NIAID's AIDS vaccine program.

But this system has allowed research to "drift," says Duke University's Dani Bolognesi, who is chairing an NIH vaccine-review committee composed of prominent scientists. Its task: correct the drift that causes problems big and small. One glitch is that animal testing is not standardized. Researchers use different viral strains and routes of transmission to "challenge" vaccinated primates, which makes it hard to compare vaccine candidates and immune responses.

More disturbing is that critical questions are not getting answered. Bolognesi says "very little attention" has been paid to cytotoxic immunity, and "much too much" on the probably unattainable goal of sterilizing immunity. He calls for "better steering," perhaps with input from scientists in industry and academia—yet "very definitely involving investigator-initiated research."

Dana Cappiello (right), and Kathy Scrutchfield, founder of Until There's a Cure Foundation

MARC GELLER

Hilleman, who is also on the review committee, would prefer a more radical solution. Isolated in their separate laboratories, individual scientists cannot see the big picture, he says, so they "don't know what the hell needs to be done." He maintains that the best way to fill in the "the great big blanks of knowledge" is to invest a committee of top scientists with the power of "central direction, central tracking," and give them the money to contract out for work they themselves cannot do. His models? The March of Dimes, which conquered polio, and the military's vaccine programs during World War II. But even Hilleman thinks trying to centralize NIH research is as futile as "trying to rearrange the bones on a dead horse." NIH's core constituency—academic scientists—would mutiny: "Those guys want total academic freedom."

They also want an emphasis on "basic" science. Skeptics see careerism, because such research leads to articles in prestigious journals and academic tenure. But it can also result in critical discoveries. The holy grail is finding the "correlates of immunity," biological mechanisms that protect against HIV or, like smoke to fire, "correlate" with protection. If they could be discovered, then "we would design a vaccine around them," says Hilleman.

But the search could take decades. Indeed, in a chicken-and-egg paradox, finding what protects people may not be possible until there are protected people to study. "The ideal way" to discover the correlates of immunity, says NIAID's Fast, is to conduct "a whole bunch of vaccine efficacy trials that induce different kinds of immune responses, and see what works." But these trials depend on having vaccine candidates, which in turn depends largely on the kind of applied, empirical research NIH scientists disdain.

The consequences can be shocking. Vaccines for several diseases are made from killed virus, and this strategy has produced encouraging results with HIV's simian cousin, SIV. But it's hard to inactivate HIV and retain important "antigens," which stimulate the immune system. Peer review panels keep rejecting proposals to solve this problem, laments John Killen, director of NIAID's division of AIDS, because they don't test "a captivating hypothesis that will advance fundamental knowledge."

So even though, as Killen puts it, "one can make a compelling case that whole-killed virus ought to be developed, that we ought to pursue it very, very aggressively," the NIH has neglected this classic and potentially effective vaccine strategy.

Last year, the army picked up the slack, and is now doing the necessary gruntwork to make a whole-killed-virus vaccine. ("If you're going to win a war," says Hilleman, "you better not have diseases holding you back.") Unfortunately, the army's small AIDS research budget is in peril. Congress might slash it by as much as 75 per cent, despite the army's proud history of developing vaccines for diseases such as typhoid and yellow fever. Here is a catch-22 that symbolizes the government's AIDS vaccine failures: The army, the only organization with the mandate to actually make a vaccine, doesn't have enough resources. But the NIH, which has more resources than any biomedical institution in the world, doesn't have its eyes on the prize.

—*M.S.*

treatment still garners more than twice as much money as vaccines—and surely part of the reason more drugs are ready for testing is that they have received the lion's share of resources.

How were these priorities set? "I remember myself in front of the Congress, saying, 'What we really need to do is basic research, we need to develop a vaccine,' " says Fauci. "And the Congress beat me over the head, saying, 'How many people are in clinical trials? How many people are getting this drug? Is AZT being made available to all these people?"

The desire to save those already infected was, in the words of Martin Delaney, founder of the AIDS advocacy group Project Inform, "appropriate and heroic." But it also demonstrates how politics drives NIH research. Fighting for their lives, people with HIV form an intensely motivated and compelling constituency. But people not yet infected are very hard to mobilize. Lacking a constituency, the best chance for ending the epidemic has gotten the least amount of NIH money.

Vaccines are the most cost-effective public health measure ever invented, but they generate little profit. The leading ulcer medication does better than all vaccines combined.

Has there ever been a protest about vaccines? ACT UP's Luis Santiago, one of a handful of activists who have paid attention to the issue, thinks for a moment and replies, "No, I don't think so."

There hasn't been much insider agitation, either. Medical watchdogs, such as Project Inform and the Treatment Action Group, monitor vaccines, but not as closely as they do treatments, and certainly not as aggressively. Over the last three years, the American Foundation for AIDS Research has given about 10 per cent of its grants to vaccine-related activities. The AIDS Action Council has produced a guide to navigating the ethical minefield of human trials, as has Gay Men's Health Crisis. But these actions pale when compared to the immense efforts on therapy and behavioral prevention.

GMHC and two of its largest sister agencies, AIDS Project Los Angeles and the San Francisco AIDS Foundation, are spending $5 million this year on behavioral prevention. Those campaigns employ 46 full-time staff and 385 volunteers. Yet there is not a single employee at any AIDS organization whose full-time job is to advocate for vaccine development, says David Gold, a well-connected activist and former editor of GMHC's medical newsletter *Treatment Issues*. At some organizations, certain staff members are supposed to monitor both vaccines and therapeutic drugs, which means in practice that vaccines get short shrift. Several advocates argue that vaccine science hasn't yet progressed far enough to warrant serious attention, even though the purpose of AIDS activism is to spur science, not wait for it.

Why do vaccines get so little attention? "The AIDS activist community, and particularly people doing treatment activism, are themselves HIV-infected," explains Santiago. "It's a survival fight." A similar urgency fuels behavioral prevention. Condoms can save lives right now; a vaccine can't.

"You always hear," Gold continues, "that we have a vaccine, it's prevention. That's so simplistic and so silly. We learn continually that people slip through the cracks, even when they have all the knowledge, even when they have all the psychological counseling. I'm not suggesting that vaccine research should be the main thrust of prevention. But to totally ignore it from any prevention program, well, the costs of that to people around the world are terrible and tragic."

The omission is so glaring and so illogical that it begs a deeper explanation: Pumping money into vaccines might drain it from treatment research. Gold flatly refuses to discuss which area of research is most important. He wants new money for vaccines, and says fighting over the "meager AIDS research pie" would be "the worst thing that could happen." But in this era of flat budgets and social conservatism, new money is unlikely—which means any attempt to increase vaccine spending would force wrenching triage and, possibly, bitter infighting.

Even more disturbing are the repercussions of success. The discovery of an effective vaccine could cancel the search for a cure. If most new infections ceased, what company would invest in therapeutics? By the time a cure were licensed, the market might have literally died out. A vaccine would save tens, even hundreds of millions of lives, but it might also be a death warrant for everyone already infected. In the four decades since Salk's discovery, virtually no treatment research has occurred for polio.

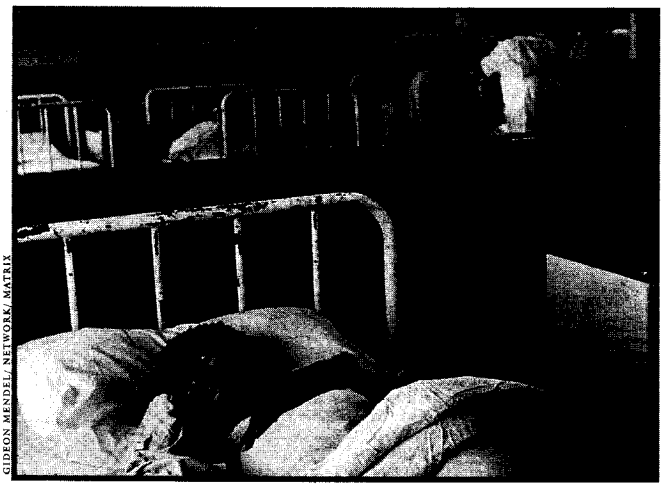
"I don't think people are making a conscious decision not to advocate for vaccines because they think it's going to hurt therapy," says William Snow, a prominent vaccine activist. Indeed, the neglect may well be unconscious, determined by guilt about the ambiguous consequences of success. Especially among HIV-negative gay men, for whom solidarity with the infected is a community obligation, pursuing a vaccine can feel like betraying one's friends and lovers.

The irony is that many of those living with the virus want a vaccine. "I'm HIV-positive," declares Snow. "And I have come to realize that, important as treatments are, they are probably never going to have an overall impact on the course of this epidemic, period. And neither is behavioral change."

Don Francis is the Larry Kramer of vaccines. A hero of Randy Shilts's *And the Band Played On*, he fought smallpox and Ebola with the Centers for Disease Control and now works for Genentech. "If one case of Ebola was brought into the U.S., we would rally everything to stop it," he tells anyone who will listen. "But even though 10,000 people get infected with HIV every day, you can count all the scientists working on an AIDS vaccine on your fingers and toes."

In 1993, Francis buttonholed Seth Berkley, the Rockefeller Foundation's associate director of health sciences. Berkley had assumed "there was a really good, coordinated effort" on a vaccine. After all, NIH has a billion-dollar AIDS budget, and researchers were attending conferences and publishing papers. But then Francis and others bent his ear.

Along with Berkley, Francis roped in Dana Cappiello, cofounder of Until There's a Cure, which sells bracelets to raise money for AIDS. With Cappiello's group underwriting travel expenses, Berkley convened an international group of scientists, pharmaceutical executives, and advocates. After the four-day conference, the Rockefeller Foundation committed to creating a "1990s version of the March of Dimes," an initiative that would coordinate academic, industrial, and government efforts worldwide to make an AIDS vaccine. It is seeking $600 million for an initial seven-year effort, and it may turn to the World Bank or the governments of wealthy countries. It has also talked with the newly formed Albert B. Sabin Vaccine Foundation (that has DNA codiscoverer James Watson on its board of trustees); that group wants to create a new kind of tax-free bond to support AIDS vaccine work.



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Can Rockefeller raise the money? It certainly has experience and credibility; in 1930 it outspent the U.S. government on medical R&D, and today it is the largest private funder of international AIDS activities. But more importantly, the toll of the epidemic may finally have reached a critical mass. Berkley notes that $600 million is "less than 1 per cent of what would be spent on AIDS prevention and care" worldwide during the same seven-year period.

"I've talked with other pharmaceutical and biotechnology companies," says Therion's Panicali, who attended the Rockefeller conference, "and I think many of us, even though we initially got into this for economic reasons, are coming to the point where we're willing to cooperate. I'm willing to share any return on an AIDS vaccine with any group that can move this thing forward. Because I know I could do a lot more if I had the resources, and I don't just mean financial, but clinical infrastructure, primates, everything. I have a lot of ideas. I have a lot of vaccines I'd like to try."

A grassroots constituency may also be growing. NIAID is enrolling 4800 people to prepare for future vaccine trials. Although this group conducts no activism, its very existence means that people across the country are thinking about vaccines. And recently, through a slew of media reports, gay men are facing up to how hard, almost impossible, it is to maintain safer sex over a lifetime.

Cappiello thinks support for an AIDS vaccine is huge. A smart marketer, she is convinced middle America is willing to mobilize behind a vaccine. Last year, her organization, which donates half its money to education and care and the rest to vaccine development, made headlines when it enlisted the first major sports team—the San Francisco Giants—to host an AIDS benefit. This year, she's added the 49ers. She has also set up a Silicon Valley Cares fundraiser, and is working on a similar idea for Wall Street.

Don Francis thinks mothers are the great untapped vaccine constituency, because "they think about the next generation." If so, Cappiello is exhibit A. Her best friend, who died of AIDS three years ago, "was Santa Claus to my kids and really involved in our family," she recalls. As his health deteriorated, Cappiello's family cared for him. "He got dementia, and he couldn't talk. It was awful. And when I saw my boys visiting him, I just didn't want them to go through that."

Cappiello is working seven days a week now, and her business may suffer. "My husband says, 'Remember when you used to make money?' " she laughs. "Well, I might have to forfeit my company. But if I can have my kids vaccinated, it'll be worth it." ❖

Research assistance: Jordan Lite